International Workshop on Recent Advances in Numerical Methods for Hyperbolic Conservation Laws and Nonlinear Time Dependent Partial Differential Equations in Honour of the 70th Birthday of Prof. Dr. Dr. hc. Eleuterio F. Toro, OBE

An ADER finite volume method for an atherosclerosis model

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POLITÉCNICA
"Ingeniamos el futuro"

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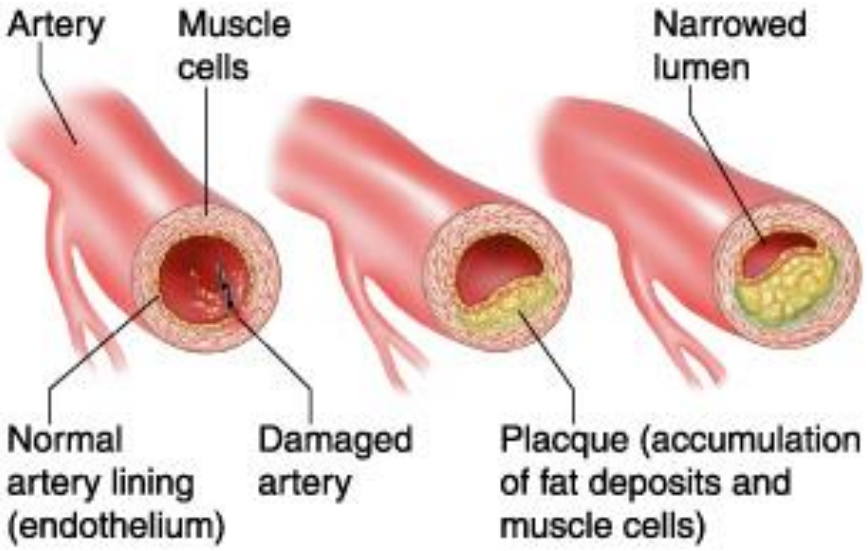
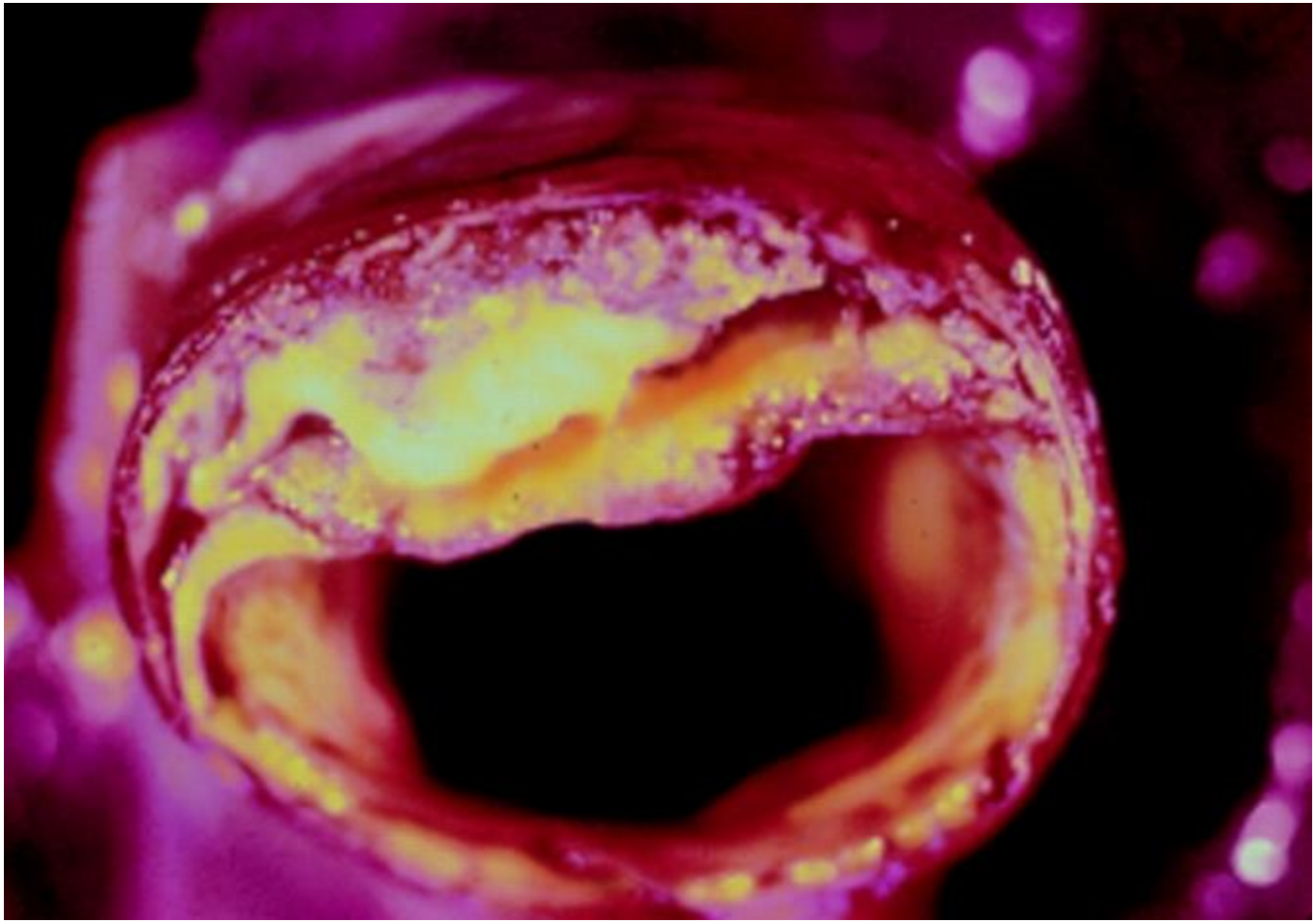
WHAT IS ATHEROSCLEROSIS ??

Is an inflammatory disease caused by the deposition of low density lipoproteins (cholesterol LDL) in the walls of the arteries.

The inflammation process is considered as a response to an injury to the vascular endothelium (as suggested by Ross et al (1973))

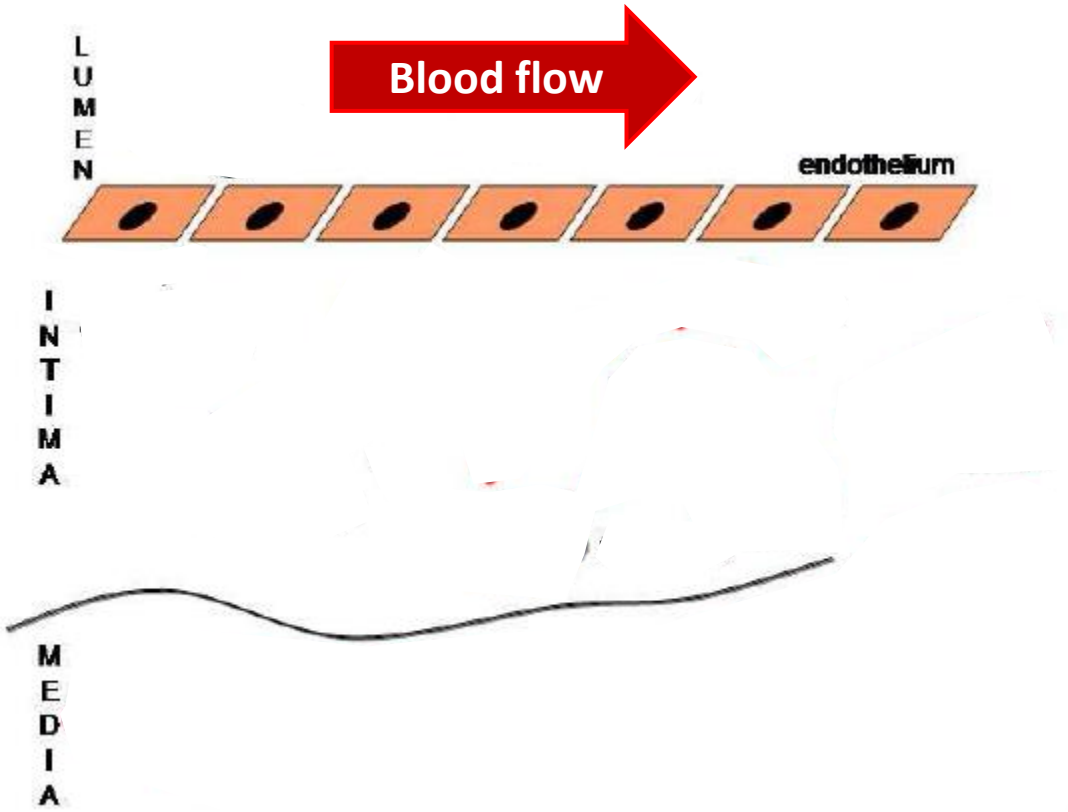


Source:
http://www.mdguidelines.com/atherosclerosis-and-arteriosclerosis/definition



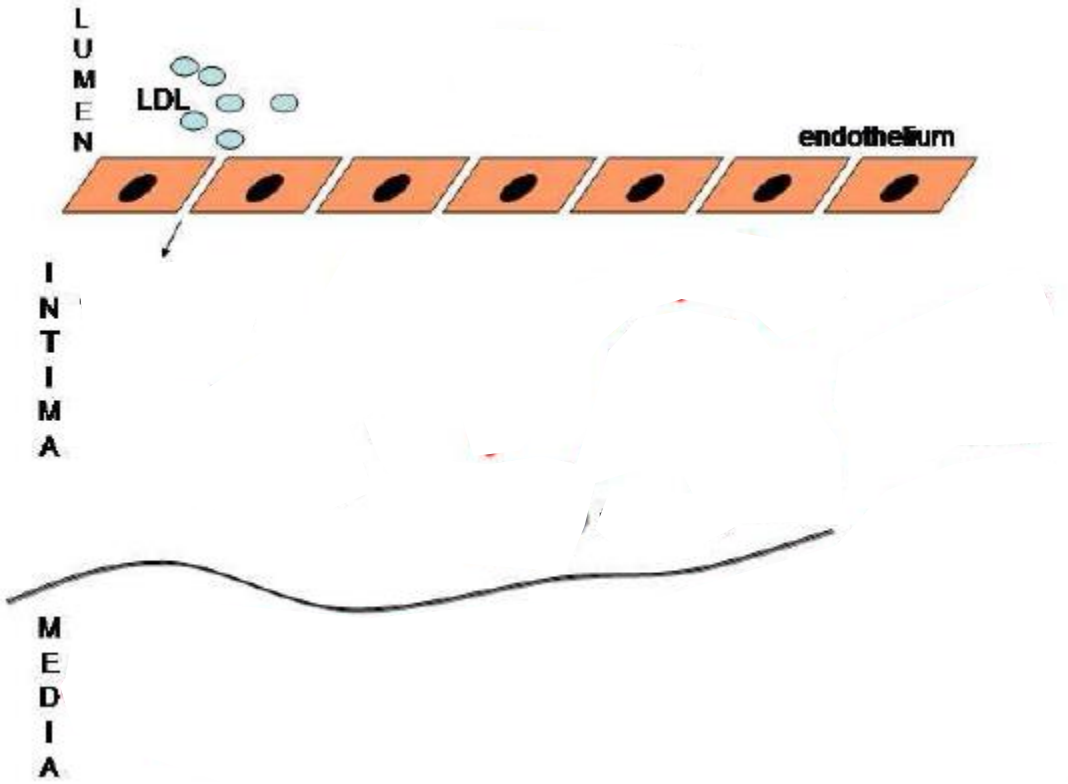
Source:
http://www.sos03.com/Diseases/Vascular/Atherosclerosis

FIRST STAGES IN ATHEROSCLEROSIS



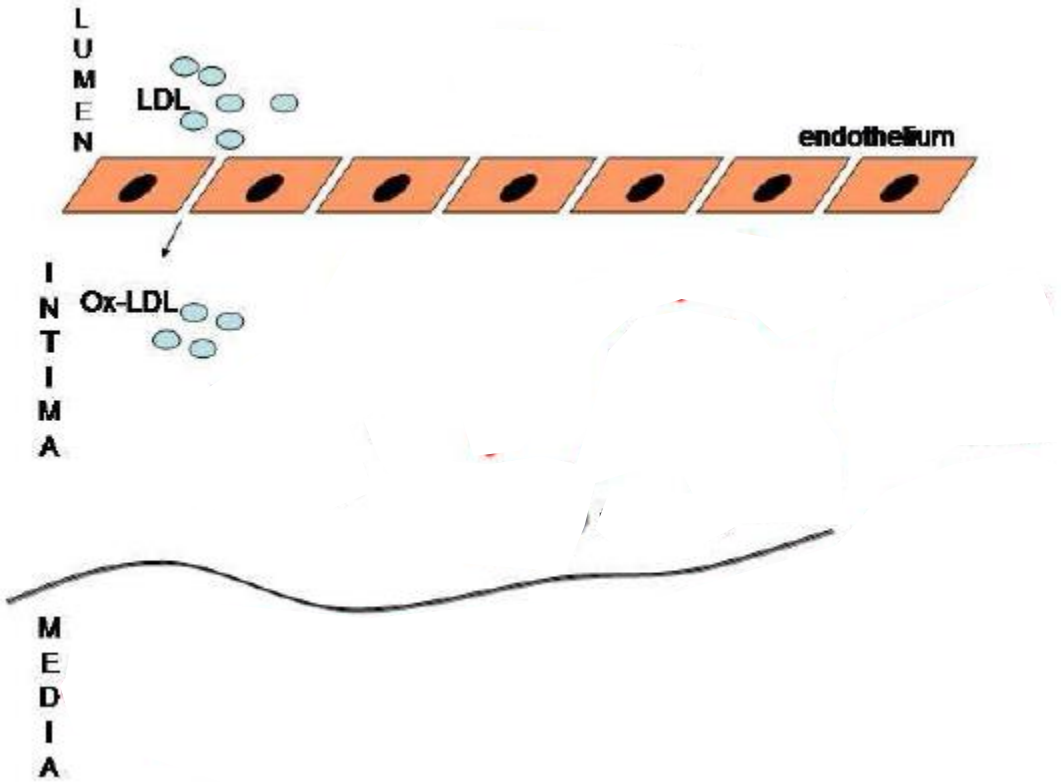
FIRST STAGES IN ATHEROSCLEROSIS

Initiation of the process: Entry of LDLs into the intima blood vessel.



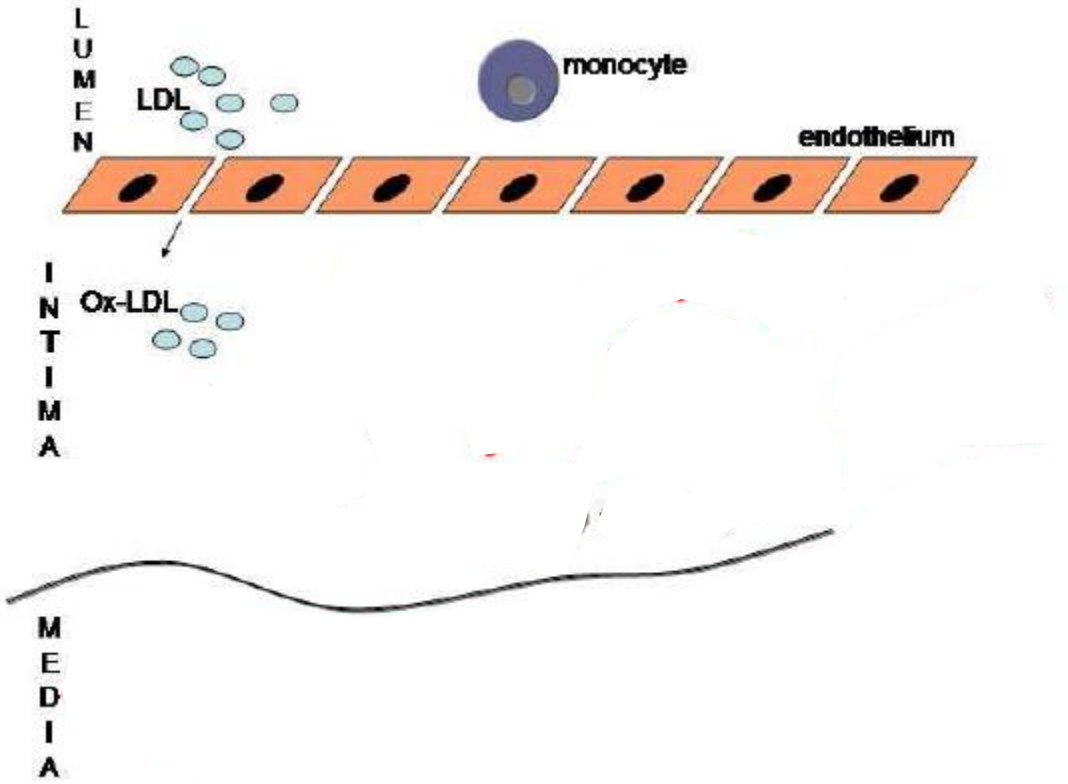
FIRST STAGES IN ATHEROSCLEROSIS

LDLs are oxidized to ox-LDL.



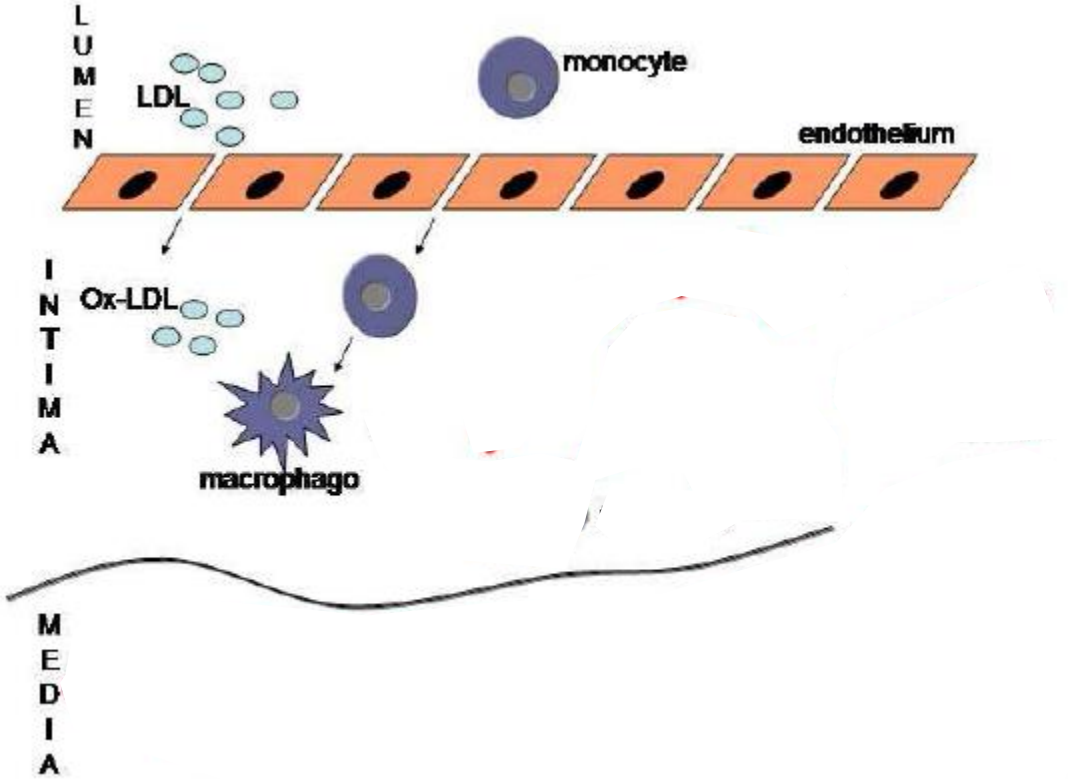
FIRST STAGES IN ATHEROSCLEROSIS

Ox-LDL triggers the recruitment of monocytes.



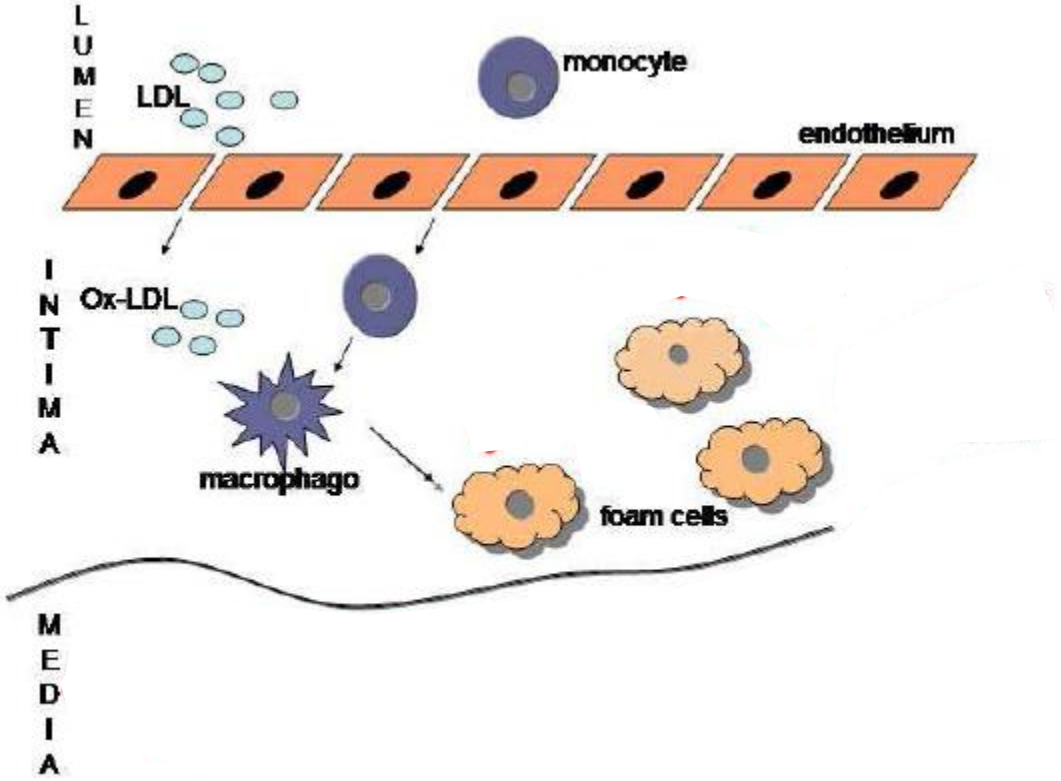
FIRST STAGES IN ATHEROSCLEROSIS

The monocytes penetrate the intima and transform to macrophages which phagocyte the ox-LDL.



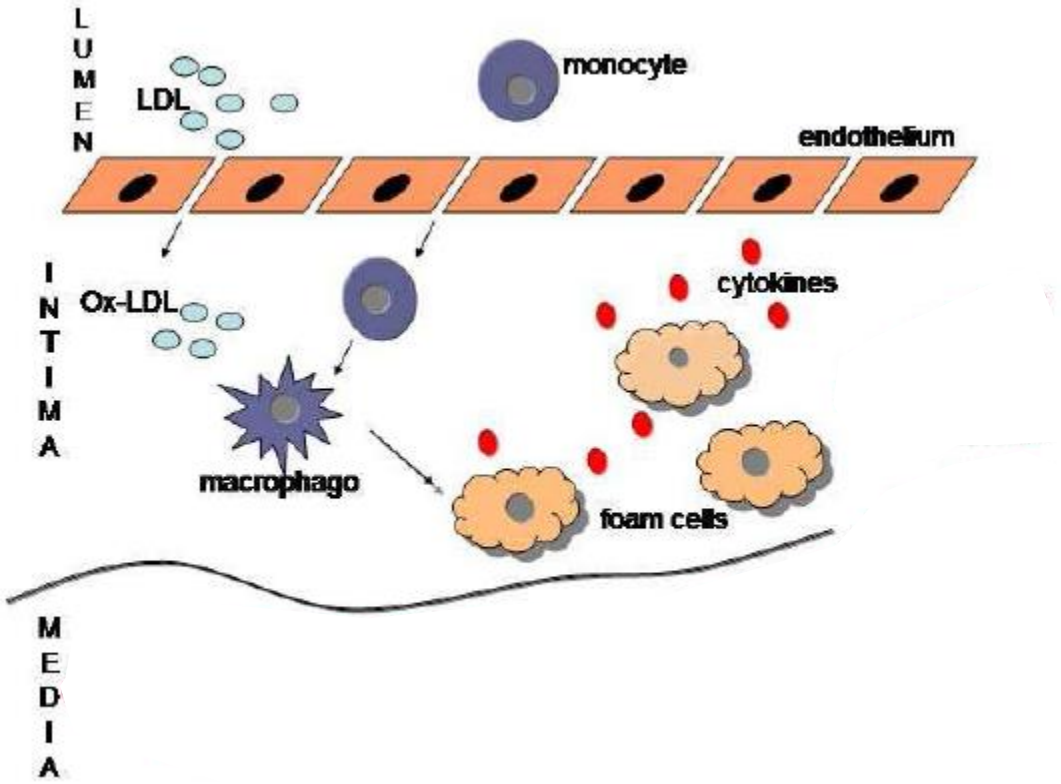
FIRST STAGES IN ATHEROSCLEROSIS

Macrophages are transformed in foam cells which have to be removed from the inmune system.



FIRST STAGES IN ATHEROSCLEROSIS

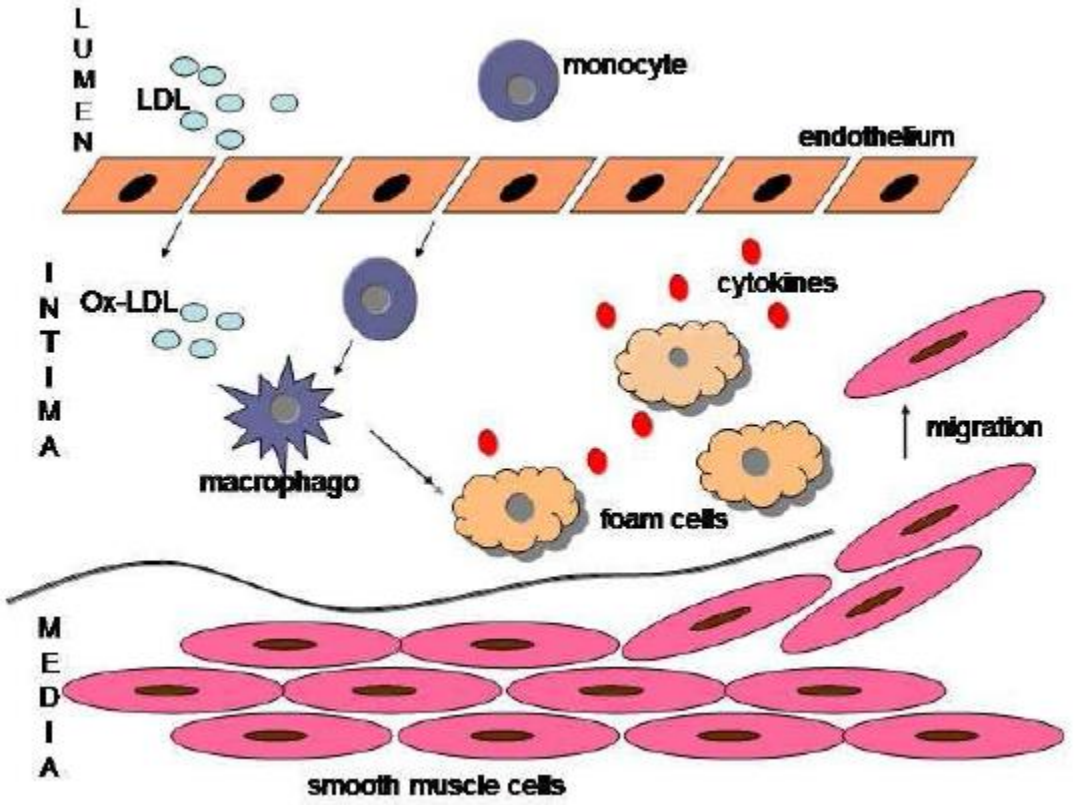
Foam cells set up a chronic inflammation by secreting pro-inflammatory cytokines (TNF-α,IL-1,…).



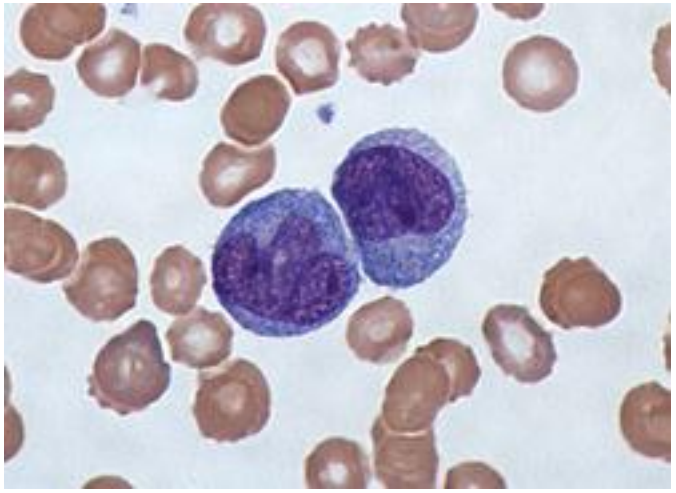
At the same time anti-inflammatory cytokines (IL-10) are produced, which inhibit the production of pro-inflammatory ones.

FIRST STAGES IN ATHEROSCLEROSIS

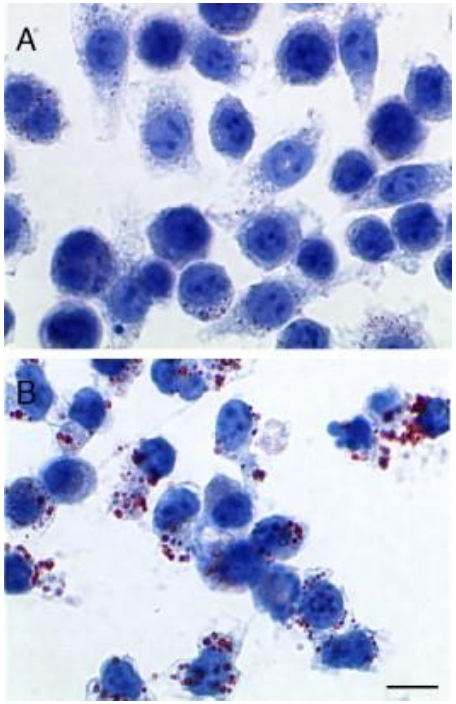
Inflammation involves proliferation and migration of muscle cells …



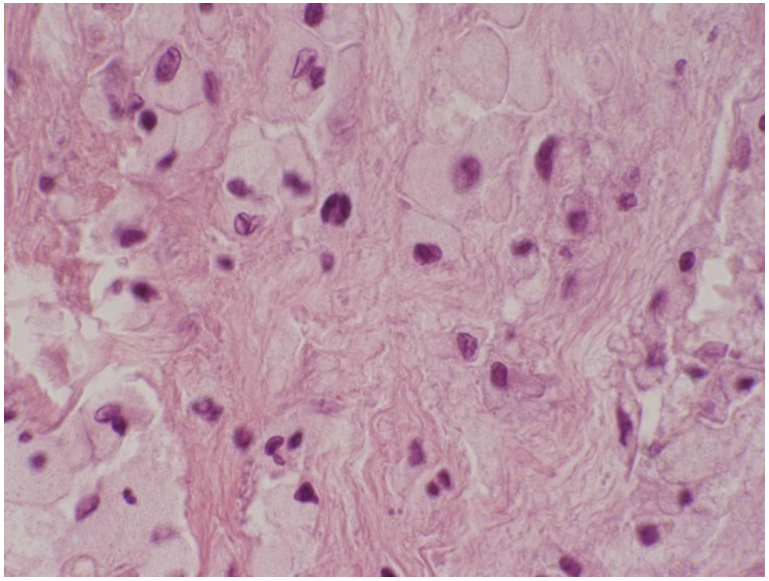
to create a fibrous cap over the lipid deposit isolating it from the blood stream.



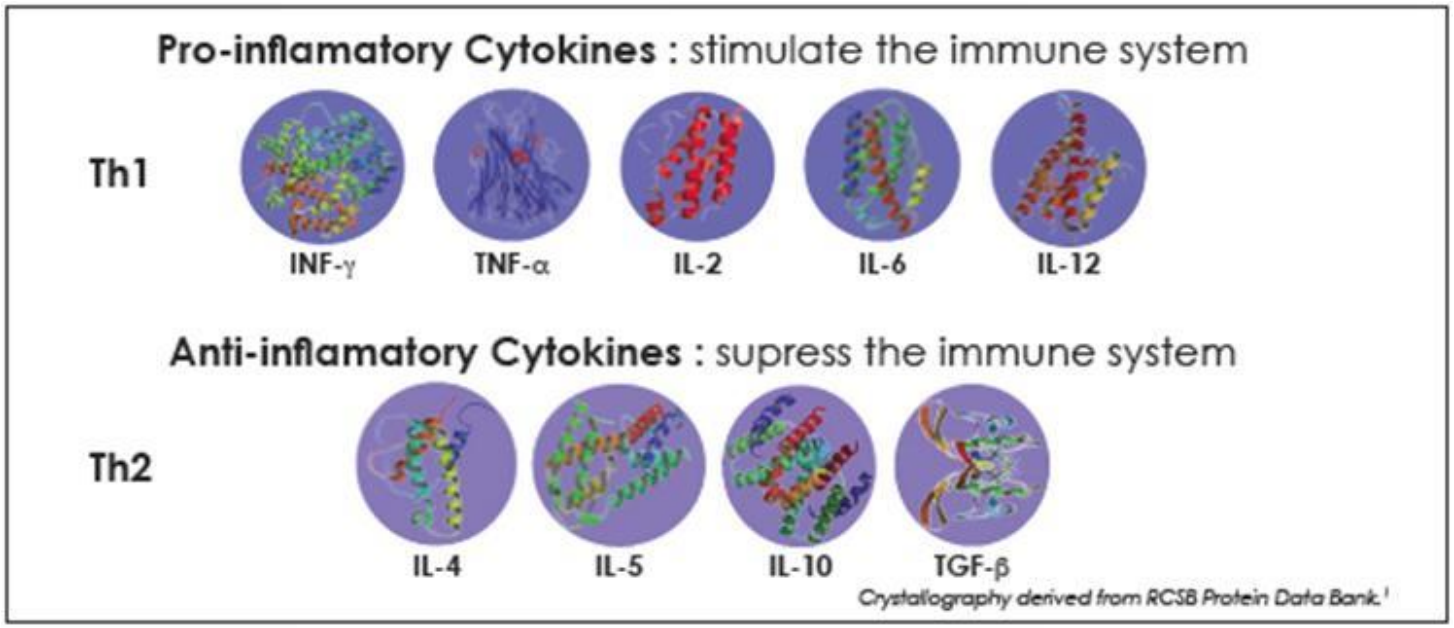
Monocytes.
(Source: Wikipedia)



Macrophages and foam cells formation.
(Source:
http://www.sciencedirect.com/science/article/pii/S1050173807000059)



Foam cells in aorta. (Source: http://www.kuma.us/index.cfm/page/daily/athero.htm)



Source: http://www.systemicenzymesupport.org/cytokines/index.htm

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Starting point

Hidalgo, A., Tello, L., Toro, E.F. *Numerical and analytical study of an atherosclerosis inflammatory disease model*. Journal of Mathematical Biology. June 2014, Volume 68, Issue 7, pp 1785–1814.

where El Khatib's model was followed…

Philos Trans A Math Phys Eng Sci. 2009 Dec 13;367(1908):4877-86. doi: 10.1098/rsta.2009.0142.

Mathematical modelling of atherosclerosis as an inflammatory disease.

El Khatib N[1], Génieys S, Kazmierczak B, Volpert V.

MATHEMATICAL MODEL

$$
\begin{cases}
\dfrac{\partial M}{\partial t} = d_1 \dfrac{\partial^2 M}{\partial x^2} + f_1(A) - \lambda_1 M\,, & x \in (0,L)\,, t > 0 \\
\dfrac{\partial A}{\partial t} = d_2 \dfrac{\partial^2 A}{\partial x^2} + f_2(A) M - \lambda_2 A\,, & x \in (0,L)\,, t > 0 \\
\dfrac{\partial M}{\partial x} = 0, \quad \dfrac{\partial A}{\partial x} = 0 \text{ on } x = 0 \text{ and } x = L \\
M(x,0) = M_0(x), \qquad A(x,0) = A_0(x).
\end{cases}
$$

(El Khatib et al 2007)

$M(x,t)$ → density of immune cells (monocytes, macrophages);
$A(x,t)$ → density of cytokines secreted by immune cells;
t → time;
x → length along wall of the artery.
d_1 ,d_2 → diffusivity of the immune cells and cytokines, respectively.
λ_1, λ_2 → rate of degradation of the immune cells and the cytokines, respectively

MATHEMATICAL MODEL

$$f_1(A) = \frac{\alpha_1 + \beta_1 A}{1 + \frac{A}{\tau_1}}$$

is the recruitment of the immune cells from the blood flow.

$$f_2(A) = \frac{\alpha_2 A}{1 + \frac{A}{\tau_2}}$$

is the cytokine production rate.

MATHEMATICAL MODEL

REMARK

In the reference: Montecinos G.I. and Toro E.F. ***Reformulations for general advection–diffusion–reaction equations and locally implicit ADER schemes***. JCP,2014;

following Cattaneo's original idea the authors present two relaxation formulations for time-dependent, non-linear systems of advection–diffusion–reaction equations. Such formulations yield time-dependent non-linear hyperbolic balance laws with stiff source terms.

MATHEMATICAL MODEL

Now we considered a modified model in which diffusion is nonlinear Porous medium-type.

$$\begin{cases} \dfrac{\partial M}{\partial t} = d_1 \dfrac{\partial^2 M^m}{\partial^2 x} + f_1(A) - \lambda_1 M\,, & x \in (0,L)\,, t > 0 \\ \dfrac{\partial A}{\partial t} = d_2 \dfrac{\partial^2 A^m}{\partial x^2} + f_2(A) M - \lambda_2 A, & x \in (0,L)\,, t > 0 \\ \dfrac{\partial M}{\partial x} = 0, \quad \dfrac{\partial A}{\partial x} = 0 \text{ on } x = 0 \text{ and } x = L \\ M(x,0) = M_0(x), \qquad A(x,0) = A_0(x). \end{cases}$$

with

$m \in \mathbb{N}$

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NUMERICAL APPROXIMATION: FV framework

$$\frac{\partial \mathbf{Q}}{\partial t} = \mathbf{D}\frac{\partial}{\partial x}\left(\alpha(\mathbf{Q})\frac{\partial \mathbf{Q}}{\partial x}\right) + \mathbf{R}(\mathbf{Q})$$

where

$$\mathbf{Q} = (M, A)^T \;,\; \mathbf{D} = \begin{pmatrix} d_1 & 0 \\ 0 & d_2 \end{pmatrix}$$

$$\mathbf{R} = (f_1(A) - \lambda_1 M,\; f_2(A)M - \lambda_2 A)^T$$

$$with\ \alpha(\mathbf{Q}) := m\mathbf{Q}^{m-1}$$

NUMERICAL APPROXIMATION: FV framework

$$\frac{\partial \mathbf{Q}}{\partial t} = \mathbf{D}\frac{\partial}{\partial x}\left(\alpha(\mathbf{Q})\frac{\partial \mathbf{Q}}{\partial x}\right) + \mathbf{R}(\mathbf{Q})$$

where

$$\mathbf{Q} = (M, A)^T \,, \mathbf{D} = \begin{pmatrix} d_1 & 0 \\ 0 & d_2 \end{pmatrix}$$

$$\mathbf{R} = (f_1(A) - \lambda_1 M,\, f_2(A)M - \lambda_2 A)^T$$

$$with\ \alpha(\mathbf{Q}) := m\mathbf{Q}^{m-1}$$

Let us consider the space-time control volume

$$V = [x_{i-1/2}, x_{i+1/2}] \times [t^n, t^{n+1}]$$

and integrate over the control volume V

$$\mathbf{Q}_i^{n+1} = \mathbf{Q}_i^n + \frac{\Delta t}{\Delta x}\left(\mathbf{G}_{i+1/2} - \mathbf{G}_{i-1/2}\right) + \Delta t \mathbf{R}_i$$

NUMERICAL APPROXIMATION: FV framework

$$\mathbf{Q}_i^{n+1} = \mathbf{Q}_i^n + \frac{\Delta t}{\Delta x}\left(\mathbf{G}_{i+1/2} - \mathbf{G}_{i-1/2}\right) + \Delta t \mathbf{R}_i$$

where

$$\mathbf{Q}_i^n = \frac{1}{\Delta x}\int_{x_{i-1/2}}^{x_{i+1/2}} \mathbf{Q}(x,t^n)dx, \quad \mathbf{G}_{i+1/2} = \frac{1}{\Delta t}\mathbf{D}\int_{t^n}^{t^{n+1}} m\mathbf{Q}^{m-1}(x_{i+1/2},t)\frac{\partial \mathbf{Q}}{\partial x}(x_{i+1/2},t)dt$$

$$\mathbf{R}_i = \frac{1}{\Delta x \Delta t}\int_{t^n}^{t^{n+1}}\int_{x_{i-1/2}}^{x_{i+1/2}} \mathbf{R}(\mathbf{Q}(x,t))dxdt$$

NUMERICAL APPROXIMATION: FV framework

The intercell flux at $x_{i+1/2}$ is given by an integral average in time of the solution

$$\mathbf{G}_{i+1/2} = \mathbf{D}\frac{1}{\Delta t}\int_0^{\Delta t} \alpha(\mathbf{Q}(x_{i+1/2},\tau))\frac{\partial \mathbf{Q}}{\partial x}(x_{i+1/2},\tau)d\tau$$

Therefore we need the values

$$\mathbf{Q}(x_{i+1/2},\tau) \equiv \mathbf{Q}_{LR}^{(0)}(\tau)$$

$$\frac{\partial \mathbf{Q}}{\partial x}(x_{i+1/2},\tau) \equiv \mathbf{Q}_{LR}^{(1)}(\tau)$$

NUMERICAL APPROXIMATION: Main ingredients

•ADER schemes were first introduced in Toro et al. 2001 for hyperbolic problems.
•Applied to reaction-diffusion:

E.F Toro and A. Hidalgo, **"ADER finite volume schemes for nonlinear reaction-diffusion equations "** APNUM, 2009.

G. Gassner, C.-D. Munz, F. Lörcher, **" A contribution to the construction of diffusion fluxes for finite volume and discontinuous Galerkin schemes "** JCP, 2007.

A. Hidalgo and M. Dumbser, **"ADER Schemes for Nonlinear Systems of Stiff Advection–Diffusion–Reaction Equations"** JSC, 2011.

NUMERICAL APPROXIMATION: Main ingredients

We wish to compute the intercell numerical flux:

$$\mathbf{G}_{i+1/2} = \frac{1}{\Delta t}\mathbf{D}\int_0^{\Delta t} m\mathbf{Q}^{m-1}\frac{\partial \mathbf{Q}}{\partial x}(0,\tau)d\tau$$

with high accuracy in time. The procedure to achieve it contains two main ingredients:

(i) a high-order nonlinear spatial reconstruction of the gradient of the solution in each cell and

(ii) the solution of the generalized (or high-order) Riemann problem at the interface of each cell.

NUMERICAL APPROXIMATION: High-order nonlinear reconstruction

We use Weighted Essentially Non Oscillatory (WENO) reconstruction (see, e.g., Balsara and Shu JCP 2000,Titarev and Toro, JCP 2005)

We need to obtain high order polynomials which allow us to achieve values and derivatives where needed.

In WENO reconstruction for an order of accuracy r we have r candidate stencils each one with r cells

$$\{S_{i-r+1}, S_{i-r+2}, \cdots, S_i\}, \{S_{i-r+2}, S_{i-r+3}, \cdots, S_{i+1}\} \cdots \{S_i, S_{i+1}, \cdots, S_{i+r-1}\}$$

For each stencil we can consider one (r-1)-th degree polynomial. Therefore we shall have r polynomials of degree (r -1)th

$$\mathbf{P}_l(x), \quad l = 0, \cdots, r-1$$

NUMERICAL APPROXIMATION: High-order nonlinear reconstruction

The reconstruction polynomial for cell i is then obtained as a convex combination of the r polynomials P_l taken with positive nonlinear weights. These weights are

$$\omega_k = \frac{\alpha_k}{\sum_{j=0}^{r-1} \alpha_j} \quad \text{with} \quad \alpha_k = \frac{d_k}{(\varepsilon + \beta_k)^p}; \qquad (k = 0,1,\ldots,r-1), (\varepsilon = 10^{-6}; \quad p = 2)$$

with smoothness indicators

$$\beta_k = \sum_{m=0}^{r-1} \int_{x_{i-1/2}}^{x_{i+1/2}} \left(\frac{d^m}{dx^m} p_k(x) \right)^2 \Delta x^{2m-1} dx \quad (k = 0,\ldots,r-1)$$

The linear weights, d_i, used in this work are based on Dumbser, Enaux, Toro (2008) where a very large weight is assigned to the central stencil and a very small linear weight is assigned to the biased ones.

NUMERICAL APPROXIMATION: FV framework

The intercell flux at $x_{i+1/2}$ is given by an integral average in time of the solution

$$\mathbf{G}_{i+1/2} = \mathbf{D}\frac{1}{\Delta t}\int_0^{\Delta t} \alpha(\mathbf{Q}(x_{i+1/2},\tau))\frac{\partial \mathbf{Q}}{\partial x}(x_{i+1/2},\tau)d\tau$$

Therefore we need the values

$$\mathbf{Q}(x_{i+1/2},\tau) \equiv \mathbf{Q}_{LR}^{(0)}(\tau)$$

$$\frac{\partial \mathbf{Q}}{\partial x}(x_{i+1/2},\tau) \equiv \mathbf{Q}_{LR}^{(1)}(\tau)$$

NUMERICAL APPROXIMATION: ADER approach

$$\mathbf{Q}_{LR}^{(0)}(\tau)$$

$$\begin{cases} \dfrac{\partial}{\partial t}\mathbf{Q}(x,t) = \mathbf{D}\dfrac{\partial}{\partial x}\left(\alpha(\mathbf{Q}(x,t))\dfrac{\partial}{\partial x}\mathbf{Q}(x,t)\right) + \mathbf{R}(\mathbf{Q}(x,t)), -\infty < x < \infty, t > 0, \\ \mathbf{Q}(x,0) = \begin{cases} \mathbf{P}_i(x) & \text{if} \quad x < 0, \\ \mathbf{P}_{i+1}(x) & \text{if} \quad x > 0. \end{cases} \end{cases}$$

where $\mathbf{P}_i$ and $\mathbf{P}_{i+1}$ are polynomials to be obtained via a reconstruction procedure (WENO in this case).

NUMERICAL APPROXIMATION: ADER approach

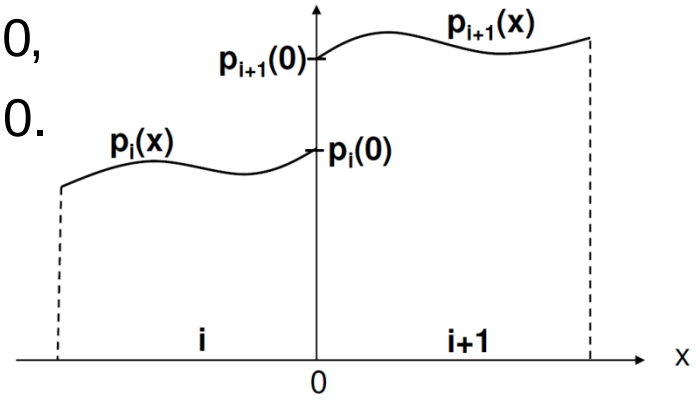
$$\mathbf{Q}_{LR}^{(0)}(\tau)$$

The sought solution is obtained using the following power series expansion

$$\mathbf{Q}_{\mathrm{LR}}^{(0)}(\tau)=\mathbf{Q}^{(0)}(0,0_{+})+\sum_{k=1}^{K}\frac{\tau^{k}}{k!}\frac{\partial^{k}}{\partial t^{k}}\partial_{x}\mathbf{Q}(0,0_{+})+\mathcal{O}(\tau^{K+1})$$

The leading term is obtained solving the linearized problem

$$\begin{cases}\dfrac{\partial}{\partial t}\mathbf{Q}(x,t)=\mathbf{D}\hat{\alpha}\dfrac{\partial^{2}}{\partial x^{2}}\mathbf{Q}(x,t),-\infty<x<\infty,t>0,\\ \mathbf{Q}(x,0)=\begin{cases}\mathbf{P}_{i}(0) & \text{if} \quad x<0,\\ \mathbf{P}_{i+1}(0) & \text{if} \quad x>0.\end{cases}\end{cases}$$



where $\hat{\alpha}=\alpha\left(\frac{1}{2}(\mathbf{P}_{i}(0)+\mathbf{P}_{i+1}(0))\right)$

NUMERICAL APPROXIMATION: ADER approach

$$\mathbf{Q}_{LR}^{(0)}(\tau)$$

The solution reads

$$\mathbf{Q}^{(0)}(0,0_{+}) = \frac{1}{2}(\mathbf{P}_{i}(0) + \mathbf{P}_{i+1}(0))$$

The high order terms are obtained using the Cauchy-Kowalewskaya procedure.

NUMERICAL APPROXIMATION: ADER approach

$$\mathbf{Q}_{LR}^{(0)}(\tau)$$

$$\frac{\partial^k}{\partial t^k}\left(\mathbf{Q}^{(0)}(0,0_+)\right) = H^{(k)}\left(\partial_x^{(0)}\mathbf{Q}(0,0_+), \partial_x^{(2)}\mathbf{Q}(0,0_+), \cdots, \partial_x^{(2k)}\mathbf{Q}(0,0_+)\right).$$

And solve the following classical Riemann problem

$$\begin{cases} \dfrac{\partial}{\partial t}\left(\dfrac{\partial^j}{\partial x^j}\mathbf{Q}(x,t)\right) = \mathbf{D}\dfrac{\partial^2}{\partial x^2}\left(\dfrac{\partial^j}{\partial x^j}\mathbf{Q}(x,t)\right), -\infty < x < \infty, t > 0, \\ \dfrac{\partial^k}{\partial x^k}\mathbf{Q}(x,0) = \begin{cases} \mathbf{P}_i^j(0) & \text{if} \quad x \to 0_-, \\ \mathbf{P}_{i+1}^j(0) & \text{if} \quad x \to 0_+. \end{cases} \end{cases}$$

Being the solution

$$\frac{\partial^m}{\partial x^m}\mathbf{Q}(0,0_+) = \frac{1}{2}\left(\frac{d^m}{dx^m}\mathbf{P}_{i+1}(0) + \frac{d^m}{dx^m}\mathbf{P}_i(0)\right).$$

NUMERICAL APPROXIMATION: ADER approach

$$\mathbf{Q}_{LR}^{(1)}(\tau)$$

$$\begin{cases} \dfrac{\partial}{\partial t}\left(\dfrac{\partial}{\partial x}\mathbf{Q}(x,t)\right) = \mathbf{D}\dfrac{\partial}{\partial x}\left(\alpha(\mathbf{Q}(x,t))\dfrac{\partial^2}{\partial x^2}\mathbf{Q}(x,t)\right) + \mathbf{R}(\mathbf{Q}(x,t)), -\infty < x < \infty, t > 0, \\ \dfrac{\partial}{\partial x}\mathbf{Q}(x,0) = \begin{cases} \dfrac{d}{dx}\mathbf{P}_i(x) & \text{if} \quad x < 0, \\ \dfrac{d}{dx}\mathbf{P}_{i+1}(x) & \text{if} \quad x > 0. \end{cases} \end{cases}$$

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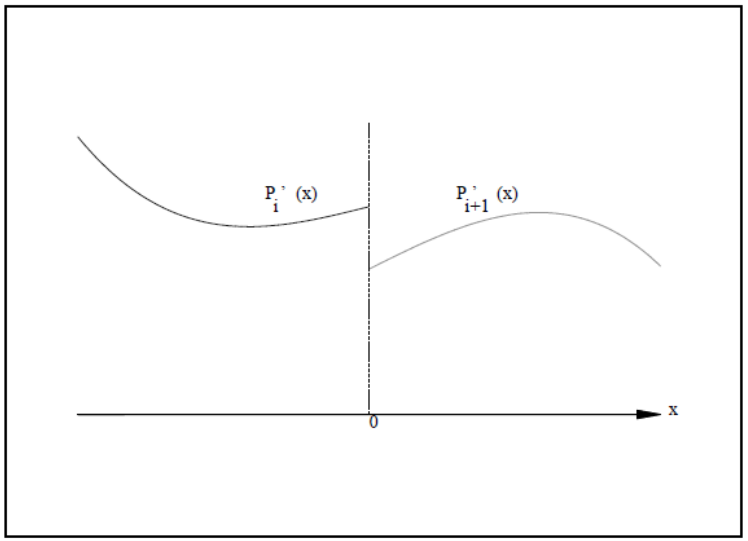
where $\hat{\alpha}=\alpha\left(\dfrac{1}{2}(\mathbf{P}_{i}(0)+\mathbf{P}_{i+1}(0))\right)$



NUMERICAL APPROXIMATION: ADER approach

The solution reads

$$\mathbf{Q}^{(0)}(0,0_+) = \frac{1}{2}\left(\frac{\mathrm{d}}{\mathrm{dx}}\mathbf{P}_i(0) + \frac{\mathrm{d}}{\mathrm{dx}}\mathbf{P}_{i+1}(0)\right)$$

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$$\frac{\partial^k}{\partial t^k}\left(\mathbf{Q}^{(1)}(0,0_+)\right)=\mathrm{P}^{(k)}\left(\partial_x^{(0)}\mathbf{Q}(0,0_+),\partial_x^{(2)}\mathbf{Q}(0,0_+),\cdots,\partial_x^{(2k)}\mathbf{Q}(0,0_+)\right).$$

And solve the following classical Riemann problems

$$\begin{cases}\dfrac{\partial}{\partial t}\left(\dfrac{\partial^j}{\partial x^j}\mathbf{Q}(x,t)\right)=\mathbf{D}\dfrac{\partial^2}{\partial x^2}\left(\dfrac{\partial^j}{\partial x^j}\mathbf{Q}(x,t)\right), -\infty<x<\infty, t>0,\\ \dfrac{\partial^k}{\partial x^k}\mathbf{Q}(x,0)=\begin{cases}\dfrac{d^j}{dx^j}\mathbf{P}_i(0) & \text{if} \quad x\to 0_-,\\ \dfrac{d^j}{dx^j}\mathbf{P}_{i+1}(0) & \text{if} \quad x\to 0_+.\end{cases}\end{cases}$$

Being the solution

$$\frac{\partial^j}{\partial x^j}\mathbf{Q}(0,0_+)=\frac{1}{2}\left(\frac{d^j}{dx^j}\mathbf{P}_{i+1}(0)+\frac{d^j}{dx^j}\mathbf{P}_i(0)\right).$$

Second ingredient: Solution of the Generalized Riemann Problem

We also need to compute the integral of the source term

$$\int_0^{\Delta t}\int_{x_{i-1/2}}^{x_{i+1/2}} \mathbf{R}(\mathbf{Q}(x,t))dxdt \approx \sum_{r=1}^{N}\omega_r \sum_{s=1}^{M}\mu_s \mathbf{R}(\mathbf{Q}(x_r,t_s))$$

In order to obtain $\mathbf{Q}(x_r,t_s)$ we apply the following Taylor expansion

$$\mathbf{Q}(x_r,\tau) = \mathbf{Q}(x_r,0) + \sum_{k=1}^{K}\frac{\tau^k}{k!}\frac{\partial^k}{\partial t^k}\mathbf{Q}(x_r,0) + \mathcal{O}(\tau^{K+1}),(r=1,\cdots,N;s=1\cdots,M)$$

and we use again Cauchy-Kowalewskaya procedure to express time derivatives as functions of space derivatives.

The leading term and high order terms are then calculated by means of spatial derivatives of the reconstruction polynomial inside the cell i.

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NUMERICAL CONVERGENCE TEST

In order to carry out a convergence test analysis we use the following auxiliary nonlinear reaction-diffusion problem:

$$\begin{cases} \dfrac{\partial q(x,t)}{\partial t} - \dfrac{\partial}{\partial x}\left(\left(1+q(x,t)\right)^2 \dfrac{\partial q(x,t)}{\partial x} \right) + 0.5q(x,t) = S(x,t), x \in (-10,10), t > 0 \\ \dfrac{\partial q}{\partial x} = 0, \text{ on } x = -10 \text{ and } x = 10 \\ q(x,0) = e^{-x^2/4} + \sin\left(\dfrac{\pi x}{20}\right) \end{cases}$$

NUMERICAL CONVERGENCE TEST

where the forcing term is:

$$S(x,t) = -e^{-\left(\frac{x^2}{4}+t\right)} - 2\left(e^{-\left(\frac{x^2}{4}+t\right)} + \sin\frac{\pi x}{20}\right)\left(-\frac{x}{2}e^{-\left(\frac{x^2}{4}+t\right)} + \frac{\pi}{20}\cos\frac{\pi x}{20}\right)^2$$

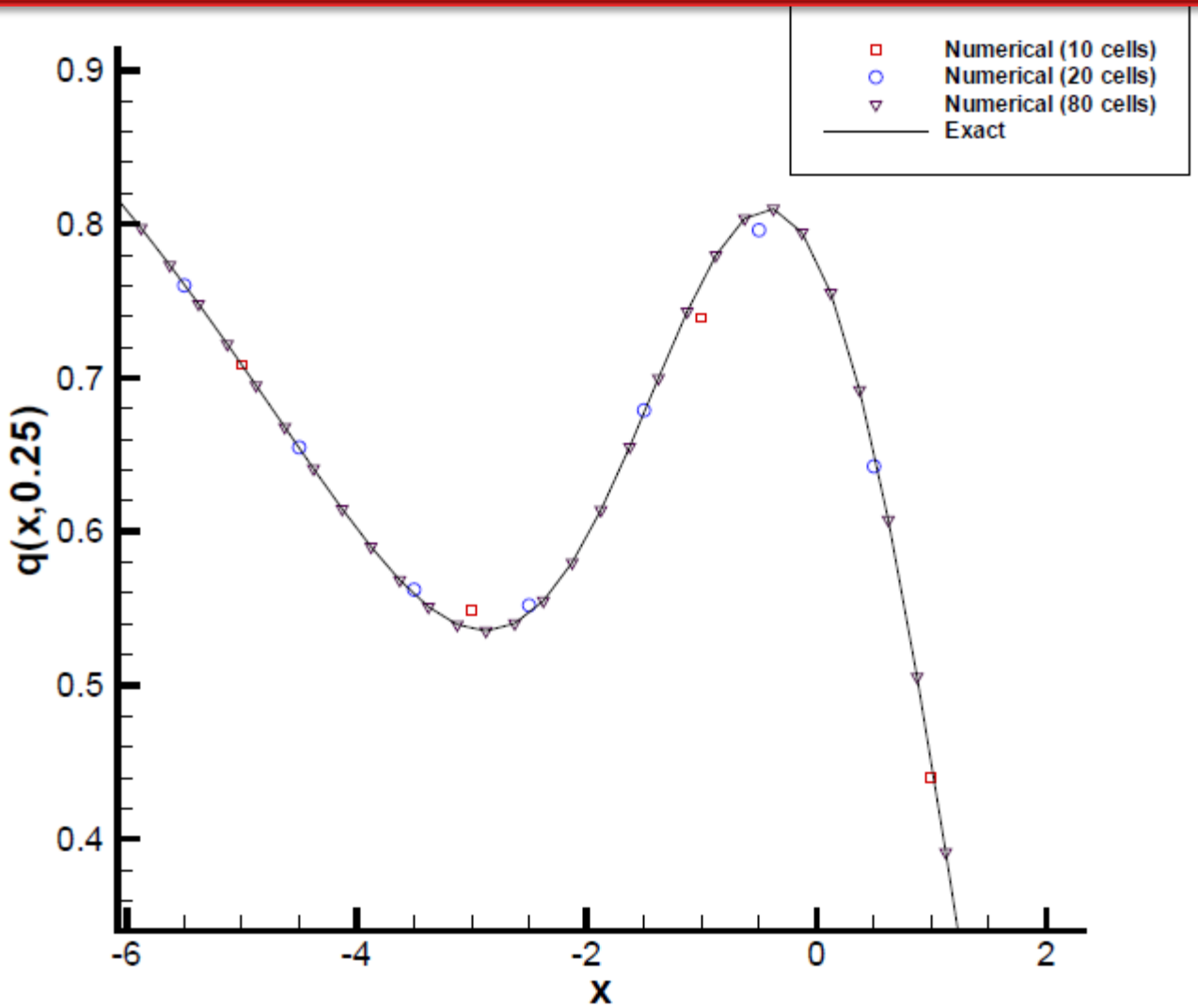
$$-\left(1+\left(e^{-\left(\frac{x^2}{4}+t\right)} + \sin\frac{\pi x}{20}\right)^2\right)\left(-\frac{1}{2}e^{-\left(\frac{x^2}{4}+t\right)} + \frac{x^2}{4}e^{-\left(\frac{x^2}{4}+t\right)} - \frac{\pi^2}{400}\sin\frac{\pi x}{20}\right)$$

$$+\frac{1}{4}\left(e^{-\left(\frac{x^2}{4}+t\right)} + \sin\frac{\pi x}{20}\right)$$

And the analytical solution is given by

$$q(x,t) = \exp\left(-\left(\frac{x^2}{4}+t\right)\right) + \sin\left(\frac{\pi x}{20}\right)$$

NUMERICAL CONVERGENCE TEST



Comparison of the analytical solution (full) and the numerical solution (symbols) for three different meshes.

NUMERICAL CONVERGENCE TEST

Convergence rates for auxiliary test problem

$Cells$	$\|\|Error\|\|_1$	$\|\|Order\|\|_1$	$\|\|Error\|\|_2$	$\|\|Order\|\|_2$	$\|\|Error\|\|_\infty$	$\|\|Order\|\|_\infty$
			$ADER-2$			
10	3.38×10^{-3}		2.59×10^{-2}		1.45×10^{-2}	
20	3.43×10^{-4}	3.30	2.96×10^{-3}	3.13	2.35×10^{-3}	2.63
40	1.54×10^{-5}	4.47	1.35×10^{-4}	4.46	8.46×10^{-5}	4.79
80	8.90×10^{-7}	4.11	7.39×10^{-6}	4.19	5.94×10^{-6}	3.83
			$ADER-3$			
10	1.56×10^{-2}		0.14×10^{0}		7.19×10^{-2}	
20	8.06×10^{-4}	4.28	1.00×10^{-3}	3.82	7.07×10^{-3}	3.35
40	9.09×10^{-6}	6.47	8.31×10^{-4}	6.91	6.69×10^{-5}	6.72
80	2.06×10^{-7}	5.47	1.68×10^{-6}	5.63	1.15×10^{-6}	5.87

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Paremeters for the numerical simulation

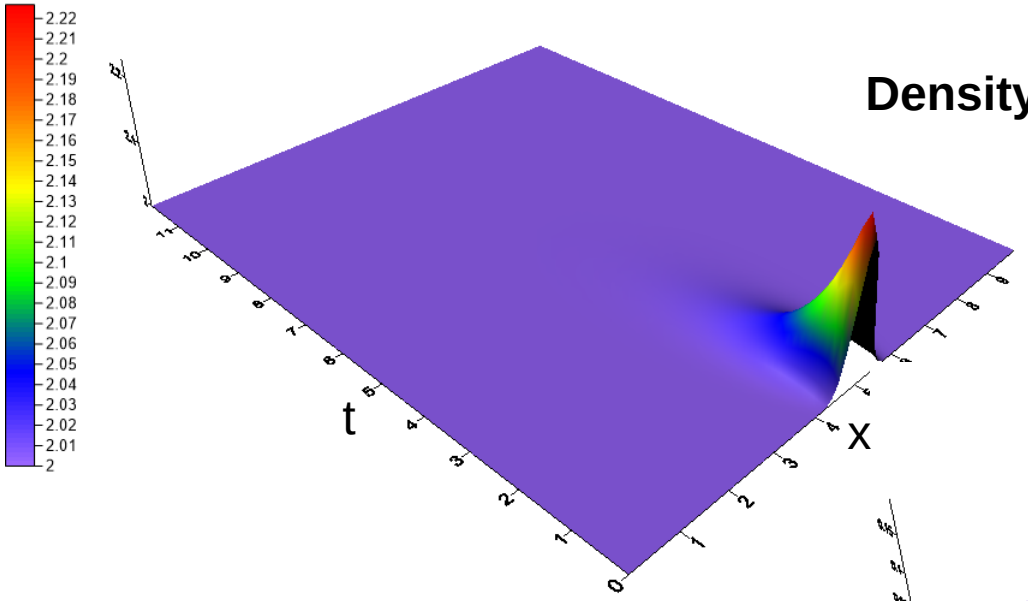
	α_1	α_2	β_1	τ_1	τ_2	λ_1	λ_2	d_1	d_2
bistable	2.	7.	8.	1.	6.5	1.	26.	0.01	0.1
monostable	2.	1.	8.	1.	42./43.	1.	1.	0.01	0.1

$\Delta x=0.01$, $\Delta t=\min(\kappa(\Delta x)^2/d_1, \kappa(\Delta x)^2/d_2)$ with $\kappa=0.45$

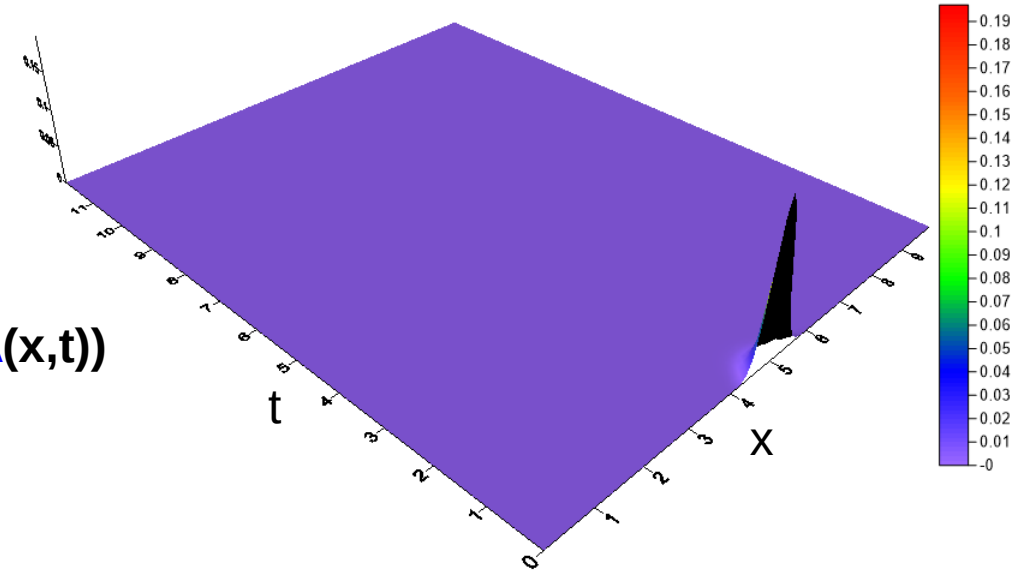
Bistable case: Two steady-state state solutions depending on the size of the initial condition.

Monostable case: One steady-state state solution .

Numerical results: Bistable case. Small perturbation of healthy steady state. Case m=2

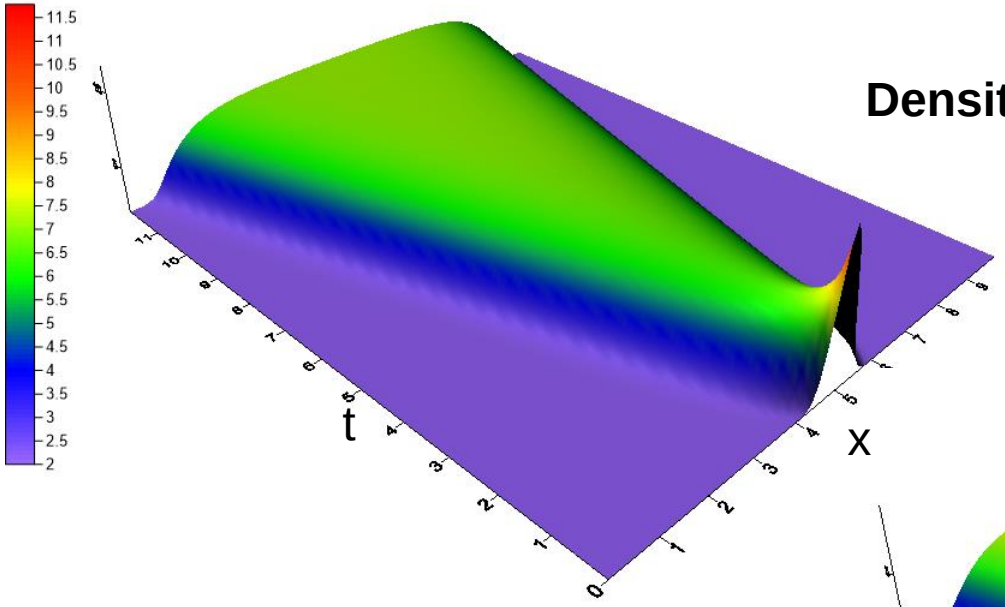


Density of immune cells (M(x,t))

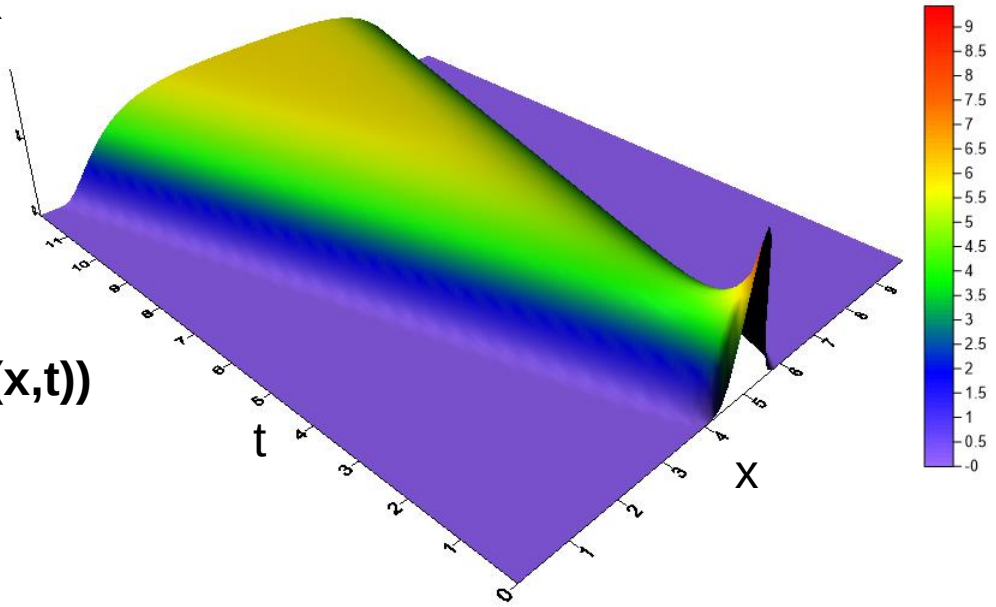


Density of cytokines (A(x,t))

Numerical results: Bistable case. Large perturbation of healthy steady state. Case m=2

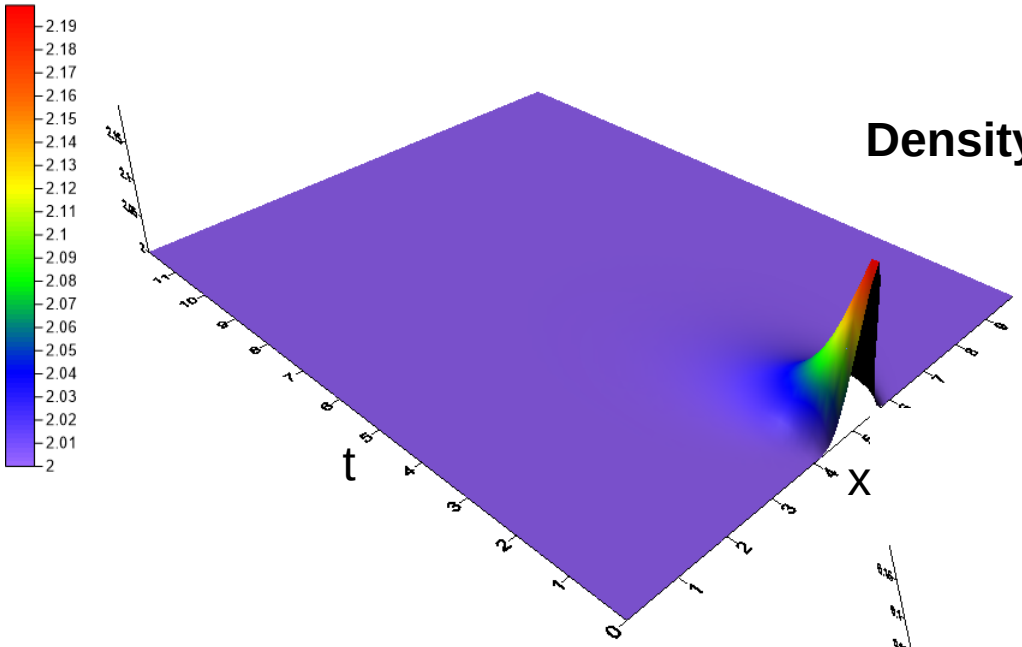


Density of immune cells (M(x,t))

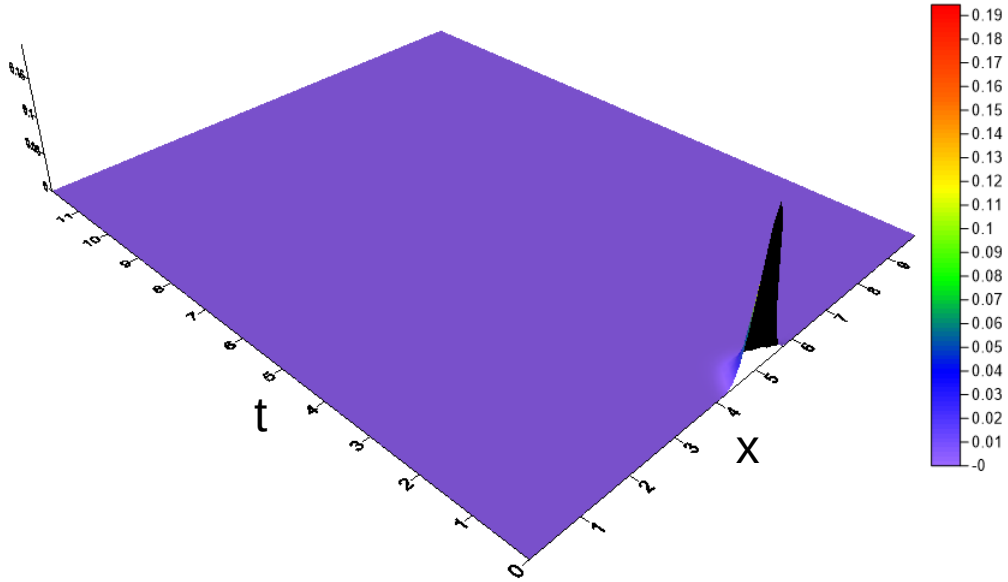


Density of cytokines (A(x,t))

Numerical results: Bistable case. Small perturbation of healthy steady state. Case m=3

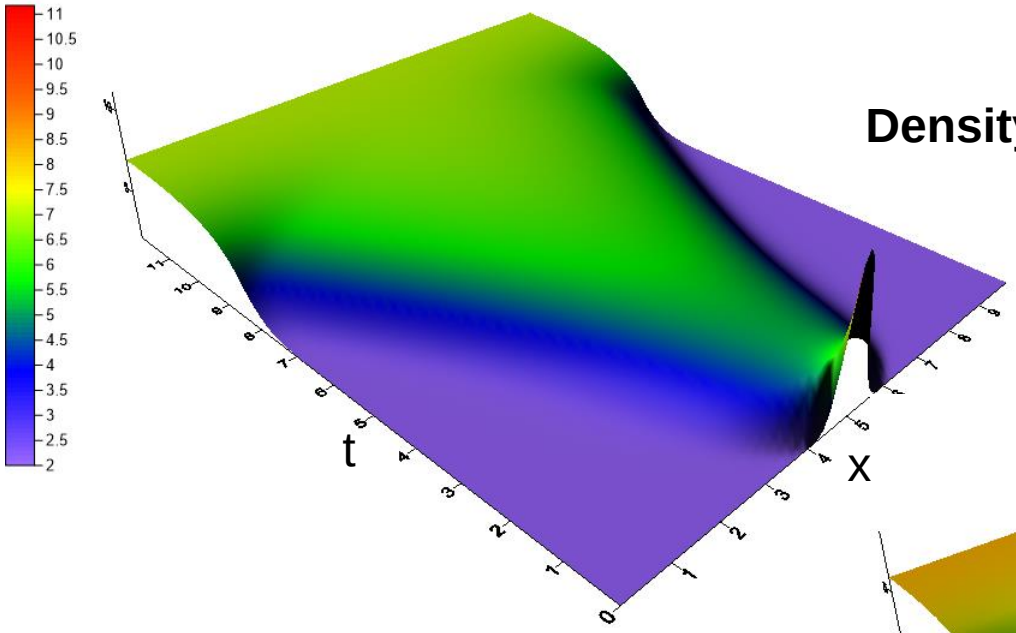


Density of immune cells (M(x,t))



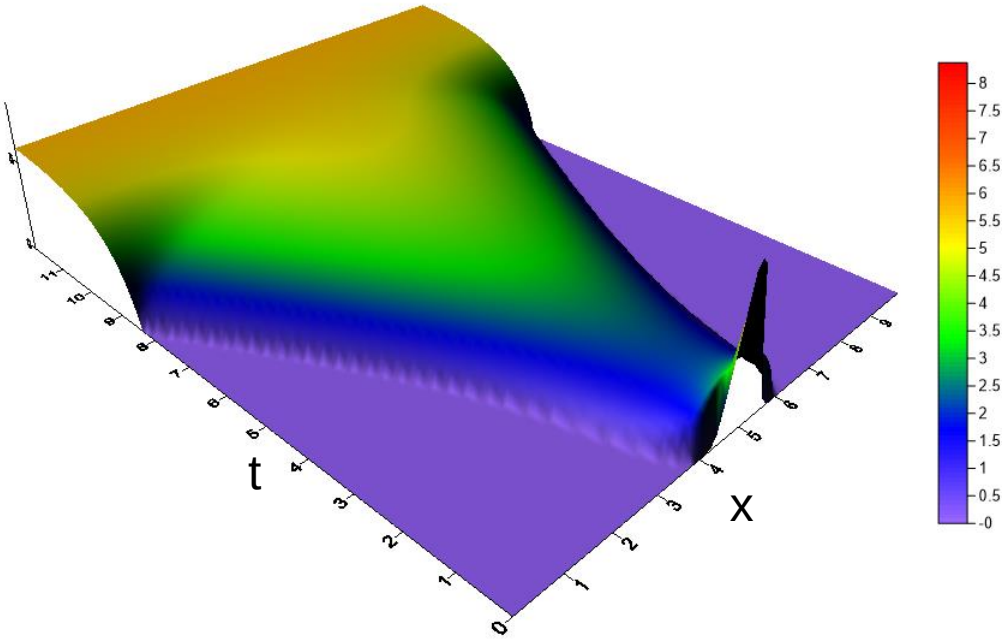
Density of cytokines (A(x,t))

Numerical results: Bistable case. Large perturbation of healthy steady state. Case m=3



Density of immune cells (M(x,t))

Density of cytokines (A(x,t))



CONTENTS

Characterization of initial conditions in the phase plane

- For the computational problem we therefore define the region of interest as the rectangle

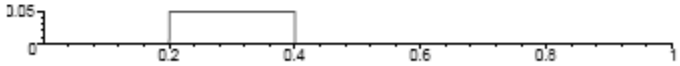
$$\mathcal{R} = \{(A, M) : 0 \leq A \leq \frac{\beta_1 \tau_1 \alpha_2 \tau_2}{\lambda_1 \lambda_2}, \quad \frac{\alpha_1}{\lambda_1} \leq M \leq \frac{\beta_1 \tau_1}{\lambda_1}\}.$$

- We consider a very large number of initial data and compute their ω-limit. To find the steady state solutions of (P) we compute the L^2-norm of the difference between $(M(x, t_k), A(x, t_k))$ and $(M(x, t_{k+1}), A(x, t_{k+1}))$. When the difference is small (less than a prescribed small positive tolerance: 2×10^{-6}) we assume we are close enough to the ω-limit.
- We use ADER finite volume method with WENO reconstruction to characterise the initial data leading to a disease equilibrium or a healthy equilibrium when the parameters are chosen in the bistable case. (Toro (2001), Toro, Hidalgo (2009)).

Characterization of initial conditions in the phase plane

$$M_i^0(x) = 2 + (i - \frac{1}{2})h + \epsilon\chi_S(x) \qquad A_j^0(x) = 0 + (j - \frac{1}{2})k + \epsilon\chi_S(x)$$

where $\epsilon = 0.05$ and $\chi_S(x)$ is the characteristic function of the interval $S = (0.2, 0.4)$. Every initial datum $(M_i^0(x), A_j^0(x)$ is identified with the centre (A_j, M_i) of every square.



Prescribed (M_i^0, A_j^0), tol

for $i = 1, n$

for $j = 1, m$

$\epsilon_1 = \epsilon_2 = 2 * tol$

while ($\epsilon_1 > tol$ or $\epsilon_2 > tol$) do

1. compute (M_i^{k+1}, A_j^{k+1})
2. $\epsilon_1 := \|M_i^{k+1} - M_i^k\|$
   $\epsilon_2 := \|A_j^{k+1} - A_j^k\|$
3. $M_i^k := M_i^{k+1}$
   $A_j^k := A_j^{k+1}$

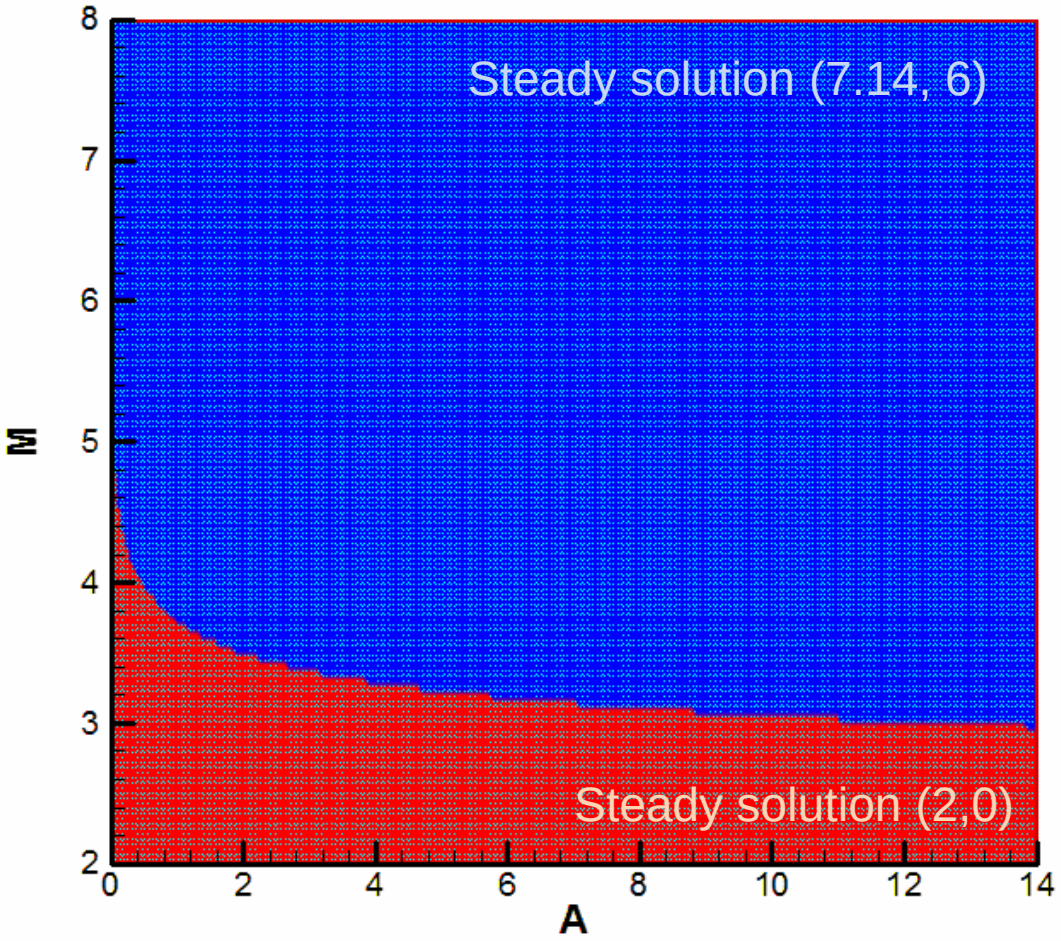
end

end

end

$$\Delta M := ||\mathbf{M}^{n+1} - \mathbf{M}^n||_2$$

$$\Delta A := ||\mathbf{A}^{n+1} - \mathbf{A}^n||_2$$



Colors depend on the ω-limit of the initial data. The upper region represents the initial data in the chosen family of every example which evolve to the disease steady state. The lower region represents the initial data in the chosen family of every example which evolve to the healthy steady state.

This task is computer-intensive since it implies the computation of the steady state solution using the iterative procedure for 96x224=25088.

SOME ASPECTS OF THE ANALYTICAL STUDY

We have proved some results regarding some properties of solutions of (P) and their evolution.

Proposition 1 *For every initial datum* $(M_0(x), A_0(x))$ *in the rectangle*

$$[\frac{\alpha_1}{\lambda_1}, \frac{\beta_1\tau_1}{\lambda_1}] \times [0, \frac{\beta_1\tau_1\alpha_2\tau_2}{\lambda_1\lambda_2}] \subset L^\infty(\Omega) \times L^\infty(\Omega)$$

the corresponding solution $(M(x,t), A(x,t))$ *of (P) verifies:* $\frac{\alpha_1}{\lambda_1} \leq M(x,t) \leq \frac{\beta_1\tau_1}{\lambda_1} \qquad 0 \leq A(x,t) \leq \frac{\beta_1\tau_1\alpha_2\tau_2}{\lambda_1\lambda_2}.$

Proposition 2 *Every stationary solution* $(M(x), A(x))$ *verifies:*

$$\frac{\alpha_1}{\lambda_1} \leq M(x) \leq \frac{\beta_1\tau_1}{\lambda_1} \qquad 0 \leq A(x) \leq \frac{\beta_1\tau_1\alpha_2\tau_2}{\lambda_1\lambda_2}.$$

Proposition 3 *Let $(M_\infty(x), A_\infty(x))$ be a solution of the stationary problem (P_∞) and $(M(x,t), A(x,t))$ a solution of the parabolic problem (P) with initial datum $M(x,0) = M^0(x)$, $A(x,0) = A^0(x)$ verifying*

$$M^0(x) \leq M_\infty(x), \qquad A^0(x) \leq A_\infty(x). \tag{23}$$

Then

$$M(x,t) \leq M_\infty(x), \qquad A(x,t) \leq A_\infty(x). \tag{24}$$

Proposition 4 *Let $(M(x,t), A(x,t))$ and $(\hat{M}(x,t), \hat{A}(x,t))$ be the solutions of (P) with initial data $(M_0(x), A_0(x))$ and $(\hat{M}_0(x), \hat{A}_0(x))$. If $M_0(x) \leq \hat{M}_0(x)$ and $A_0(x) \leq \hat{A}_0(x)$ a.e. $x \in \Omega$ then $M(x,t) \leq \hat{M}(x,t)$ and $A(x,t) \leq \hat{A}(x,t)$ a.e. $(x,t) \in \Omega \times (0, +\infty)$.*

Reference (for the linear diffusion case): Hidalgo, A., Tello, L., Toro, E.F. "Numerical and analytical study of an atherosclerosis inflammatory disease model", Journal of Mathematical Biology.
June 2014, Volume 68, Issue 7, pp 1785-1814 .

CONTENTS

2D MATHEMATICAL MODEL

$$f_1(A) = \frac{\alpha_1 + \beta_1 A}{1 + \frac{A}{\tau_1}}$$

$$\frac{\partial M}{\partial y} = \varepsilon \frac{f_1(A)}{d_1}; \quad \frac{\partial A}{\partial y} = 0$$

$$\frac{\partial M}{\partial x} = 0 \qquad \frac{\partial A}{\partial x} = 0$$

$$\frac{\partial M}{\partial x} = 0 \qquad \frac{\partial A}{\partial x} = 0$$

$$\frac{\partial M}{\partial y} = \frac{\partial A}{\partial y} = 0$$

We take ε=0.1 and L=1

2D MATHEMATICAL MODEL

$$\frac{\partial M}{\partial t} = d_1 \Delta M + f_1(A) - \lambda_1 M \,, \qquad (x,y) \in (0,1)\times(0,0.1)\,, t>0$$

$$\frac{\partial A}{\partial t} = d_2 \Delta A + f_2(A) M - \lambda_2 A, \qquad (x,y) \in (0,1)\times(0,\varepsilon)\,, t>0$$

$$\frac{\partial M}{\partial y}(x,0,t) = \frac{\partial A}{\partial y}(x,0,t) = 0, \qquad x \in (0,1)\,, t>0$$

$$\frac{\partial M}{\partial x}(0,y,t) = \frac{\partial A}{\partial x}(0,y,t) = \frac{\partial M}{\partial x}(1,y,t) = \frac{\partial A}{\partial x}(1,y,t) = 0, \qquad y \in (0,\varepsilon)\,, t>0$$

$$\frac{\partial M}{\partial y}(x,\varepsilon,t) = \frac{\varepsilon}{d_1} f(A); \;\; \frac{\partial A}{\partial y}(x,\varepsilon,t) = 0, \qquad x \in (0,1)\,, t>0$$

$$M(x,y,0) = M_0(x,y), A(x,y,0) = A_0(x,y), \qquad (x,y) \in (0,1)\times(0,\varepsilon)\,.$$

2D MATHEMATICAL MODEL

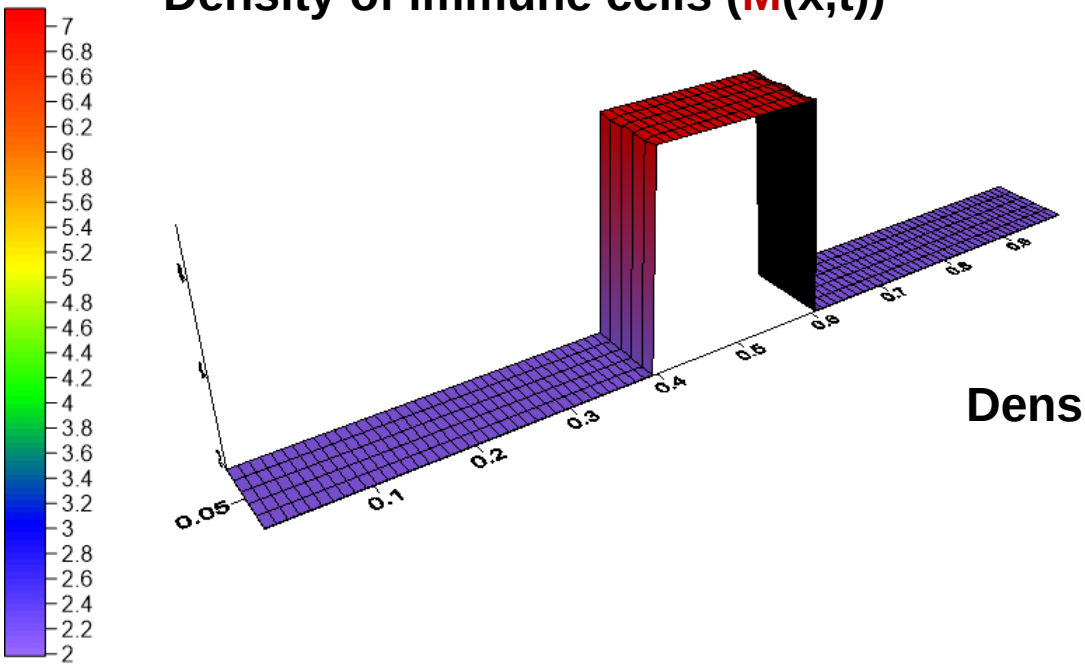
NUMERICAL METHOD: FINITE VOLUMES WITH WENO-5 RECONSTRUCTION AND RUNGE-KUTTA TVD IN TIME

Remark:

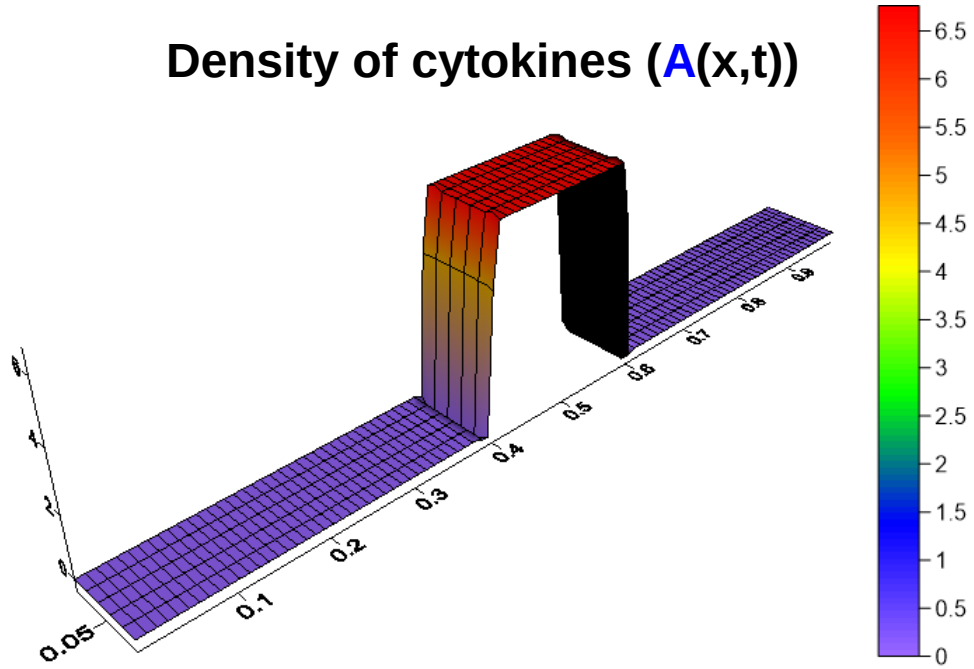
- **2D WENO reconstruction performed dimension-by-dimension**
  V.A. Titarev & E.F. Toro. *Finite-volume WENO schemes for three-dimensional conservation laws*. JCP, 2001.
  M. Dumbser, O. Zanotti, A. Hidalgo & D.S. Balsara. *ADER-WENO finite volume schemes with space–time adaptive mesh refinement.* JCP, 2013.

2D Numerical results: Bistable case. Large perturbation of healthy steady state.

Density of immune cells (M(x,t))

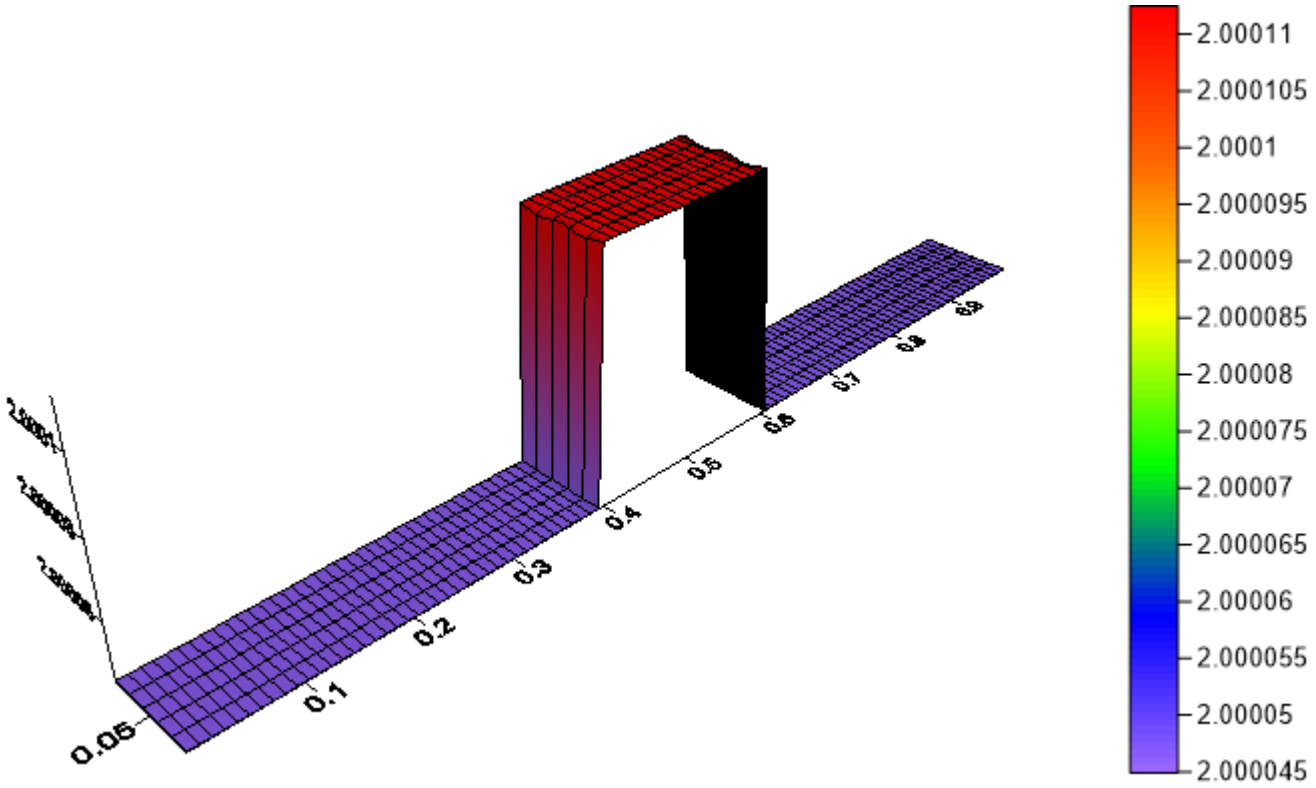


Density of cytokines (A(x,t))



2D Numerical results: Bistable case. Small perturbation of healthy steady state.

Density of immune cells (M(x,t))



Qualitative relation to experimental results

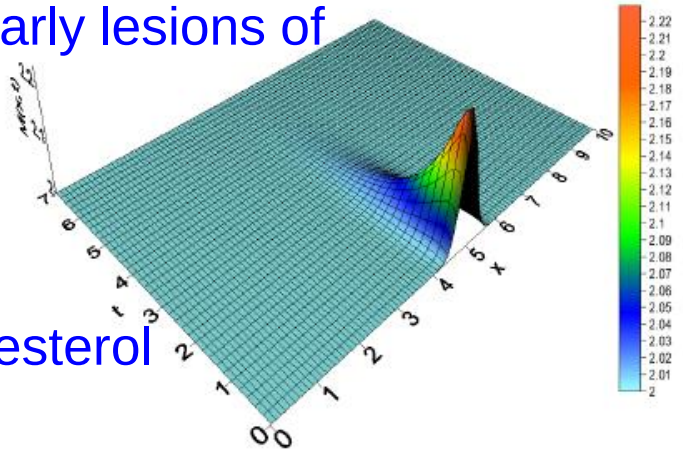
Relevant experimental results are also shown in Ikeda (2005).

Ikeda N, Torii R (2005) When Does Atherosclerosis Become Irreversible? Chronological Change from an Early to an Advanced Atherosclerotic Lesion Observed by Angioscopy. Angiology 56(4): 361-370.

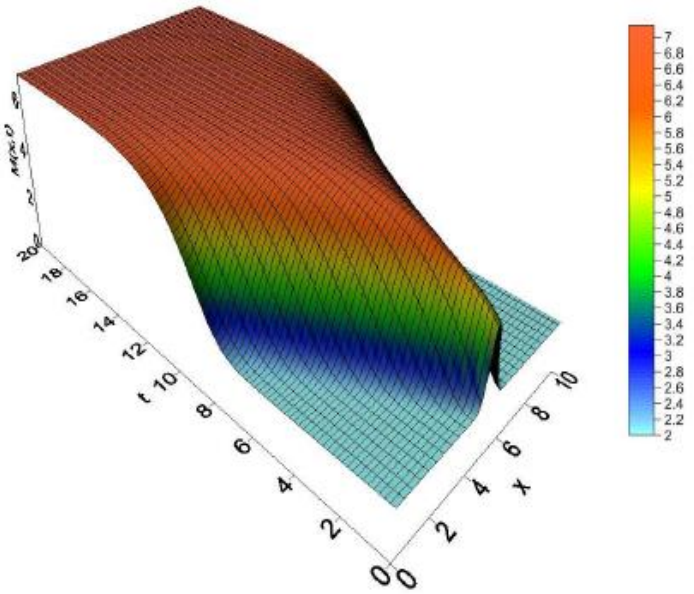
They experimented by generating atherosclerotic lesions in eleven Japanese macaques observing the progress of the lesions under changing feeding conditions.

They considered two different scenarios and these are in clear accordance with the two possible situations of our bistable case:

1. The first scenario deals with fatty streaks (early lesions of atherosclerosis developed in the aortic wall owing to cholesterol loading) that disappeared when the serum concentration of total cholesterol was reduced.



2. The second scenario involves atheroma, which are advanced lesions that gradually spread to nearby areas even though serum cholesterol was reduced. We see a clear accordance between these experimental information and the results of our bistable case



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CONCLUSIONS

•We have obtained a numerical solution of a 1D nonlinear reaction-diffusion type model, representing the initial stages of atherosclerosis, which is a variant of the one proposed by El Khatib et al (2007).
•We have also obtained the stationary solution of the 2D version of the linear model marching in time until the steady state solution.
•The numerical method used is based on FV-ADER-WENO5 for the 1D case and FV-WENO5-RK3 TVD for the 2D case.
•We have checked the numerical solution of the 1D problem using an auxiliary test problem.
•Some properties of the solution have been proved theoretically and numerically.
•Some of the numerical results reported in the present work have been qualitatively related to experimental data.

FURTHER RESEARCH

•Consideration of other phenomena, such as chemotaxis.
•Better background on the physical problem, mainly regarding to the consideration of more realistic values of the parameters.
•ADER approach in 2D.

¡¡ FELIZ CUMPLEAÑOS, TITO !!